maining solids were washed with hexanes (2 × 30 mL) and treated with 30 mL of dry benzene. The resulting white solids were removed by filtration. Solvent was removed by vacuum transfer and the resulting light cream colored solids were washed with pentane (2 × 30 mL) and vacuum dried (0.235 g, 98%): mp (sealed tube under Ar) 139-141 °C dec; IR (paraffin oil) 3065, 3040, 1580, 1565, 1480, 1435, 1430, 950, 735, 695, 685 cm^{-1}; far-IR (C_6D_6, polyethylene cell) 275 cm^{-1} (Pd-Cl); ^1H NMR (C_6D_6, 270 MHz) δ 0.66 (s, 9 H), 0.90-2.25 (m, 7 H), 5.10 (br s, 1 H), 7.00-8.00 (m, 30 H); $^{31}P\{H\}$ NMR (C_6D_6, 81 MHz) δ 24.1 (s). Anal. Calcd for $C_{46}H_{46}ClP_2Pd$: C, 68.83; H, 5.78; Cl, 4.42; P, 7.71. Found: C, 68.63; H, 5.80; Cl, 4.55; P, 7.56.

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Total Synthesis of (+)-Jatropholones A and B: Exploitation of the High-Pressure Technique

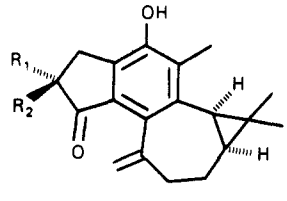
Amos B. Smith III,*[1] Nigel J. Liverton, Nicholas J. Hrib,[2] Hariharan Sivaramakrishnan, and Kevin Winzenberg

Contribution from the Department of Chemistry, The Monell Chemical Senses Center, and The Laboratory for Research on the Structure of Matter, The University of Pennsylvania, Philadelphia, Pennsylvania 19104. *Received October 16, 1985*

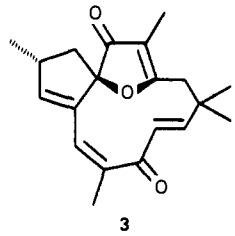
Abstract: Application of a high-pressure (5 kbar) induced Diels-Alder reaction between furan **12** and homochiral enone 6 for construction of the jatropholone skeleton is described. Subsequent aromatization, introduction of the *exo*-methylene, regioselective oxidation, and methylation afford (+)-jatropholones A and B.

Introduction and Background

In 1979, Connolly et al. at Glasgow isolated two new diterpenes termed jatropholones A and B (**1** and **2**) from *Jatropha gossypiifolia L*,[3] the same plant that yields jatrophone (**3**).[4] Unlike jatrophone, the jatropholones were found to be biologically inactive. Their novel structure however attracted our attention in that they represent a new skeletal class of diterpenes. Furthermore, we were interested in utilizing an intermediate (i.e., **4**) developed during the course of our jatrophone work,[5] which appeared ideally suited for construction of the jatropholone skeleton (vide infra.)



1 R_1 = H, R_2 = Me
2 R_1 = Me, R_2 = H



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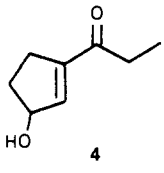

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In this, a full account,[6] we record the details of the first total synthesis of jatropholones A and B. We note in advance that the synthetic scheme, *which proved viable only through aegis of a high-pressure Diels-Alder reaction*, is short (i.e., 12 steps), reasonably efficient (6%), and establishes for the first time the absolute configuration of the jatropholones.

Prior to presentation of our synthetic analysis, it is appropriate to consider the structural features inherent in the jatropholone targets. Notable here is the close structural similarity between the jatropholones and jatrophone; note the identical peripheral array of carbons.[7] Second, jatropholones A and B are epimeric at C(2); simple base equilibration leads to their interconversion.[3] Unfortunately, as is now the norm, little chemical information concerning the jatropholones was available at the outset of this venture, aside from the usual spectral characterization and an X-ray analysis. Finally, we note with particular interest the tetracyclic array consisting of the fused 5,6,7- and 3-membered rings, a fully substituted aromatic system, and the potentially reactive C(6)-styrene functionality.

Results and Discussion

(i) A Strategy for the Construction of Jatropholones A and B. From the retrosynthetic perspective we anticipated that construction of the hexasubstituted aromatic system would be the central synthetic challenge. With this in mind, we envisioned that a Diels-Alder reaction between diene **5** and enone **6** would provide a rapid, convergent entry to the tetracyclic skeleton. Of considerable advantage here was the availability in our laboratory of enone **6**, in either racemic or homochiral form,[8] as a result of

(1) Camille and Henry Dreyfus Teacher-Scholar, 1978-1983. National Institutes of Health (National Cancer Institute) Career Development Award, 1980-1985. J. S. Guggenheim Fellow, 1985-1986.
(2) Recipient, American Cancer Society Postdoctoral Fellowship, 1982-1984.
(3) Purushothaman, K. K.; Chandrasekkharan, S.; Cameron, A. F.; Connolly, J. D.; Labbe, C.; Maltz, A.; Rycroft, D. S. *Tetrahedron Lett.* **1979**, 979.
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(5) Smith, A. B., III; Guaciaro, M. A.; Schow, S. R.; Wovkulich, P. M.; Toder, B. H.; Hall, T. W. *J. Am. Chem. Soc.* **1981**, *103*, 219.
(6) A preliminary account of this work has already appeared: Smith, A. B., III; Liverton, N. J.; Hrib, N. J.; Sivaramakrishnan, H.; Winzenberg, K. N. *J. Org. Chem.* **1985**, *50*, 3239.
(7) For a biosynthetic postulate see: (a) Adolf, W.; Hecker, E. *Experientia* **1971**, *27*, 1393. (b) Adolf, W.; Hecker, E.; Balmain, A.; Lhomme, M. F.; Nakatani, Y.; Ourisson, G.; Ponsinet, G.; Pryce, R. J.; Santhanakrishnan, T. S.; Matyukhina, L. G.; Saltikova, I. A. *Tetrahedron Lett.* **1970**, 2241.
(8) Taylor, M. D.; Minaskanian, G.; Winzenberg, K. N.; Santone, P.; Smith, A. B., III. *J. Org. Chem.* **1982**, *47*, 3960.

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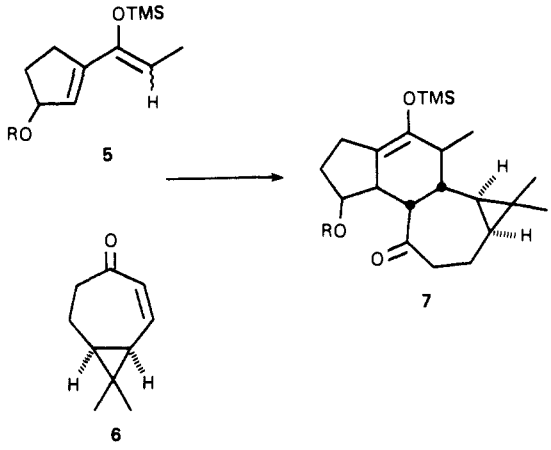
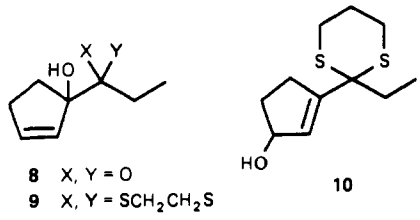


a recently completed total synthesis of hanegokedial.[9] In addition, diene **5** appeared readily available. That is, during the development of a viable synthesis of hydroxy ketone **8** for our jatrophone synthesis,[5] we observed that hydrolysis of dithiane **9** in an unbuffered system leads via an efficient acid-catalyzed rearrangement to hydroxy ketone **4**,[10] a potential precursor for diene **5**. Assuming



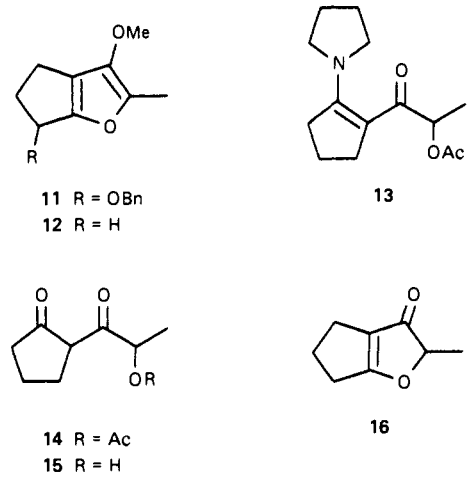
the availability of diene **5**, in conjunction with a successful Diels–Alder reaction, we anticipated that aromatization would then provide the tetracyclic skeleton of the jatropholones. Methylenation at C(6) followed by debenzylation, oxidation, and C(2) methylation would then afford jatropholones A and B.

(ii) Preparation of Diene 5. With this as background, we began the synthesis of diene **5** via addition of the lithium anion of ethyldithiane[11] to cyclopentenone, followed by an acid-catalyzed rearrangement to afford alcohol **10**. Subsequent hydrolysis of the dithiane functionality with mercuric chloride and calcium carbonate,[10] followed by formation of the ketone enolate (2.2 equiv of LDA/THF) and capture with chlorotrimethylsilane, led to diene **5**.

(iii) The Critical Diels–Alder Reaction: An Initial Setback. With the Diels–Alder components in hand, we turned to the crucial cycloaddition. Initial efforts centered on inducing the process thermally. Unfortunately, no adduct was detected in the temperature range of 100–220 °C, when the reaction was performed either neat or with benzene as the solvent. In all cases, the diene simply underwent decomposition. Attempts to use Lewis acids to induce cycloaddition[12] at or below room temperature were also unsuccessful.

(iv) Development of a Second Generation Strategy. It appeared that the lack of reactivity of diene **5** in the Diels–Alder reaction derived from one of two reasons. Either the silyl enol ether possessed the less reactive *E* configuration or the (*Z*)-diene may not be able to assume the necessary s-cis conformation at temperatures sufficiently low to avoid decomposition. Support for the former suggestion comes from studies on the *Z*/*E* ratio of acyclic ketone enolates.[13,14] In any event, we assumed that a more viable approach would entail use of a furan as the diene. In this case, the diene component would be constrained in the optimal s-cis conformation. Furthermore, aromatization of the resulting oxabicyclo[2.2.1]heptene system would be simplified[15] in that only elimination of water would be required.

With this conjecture in mind, furan **11** appeared to possess the ideal substitution pattern for entry to the jatropholone skeleton. We considered it prudent, however, to investigate a more readily available model furan (i.e., **12**) in the initial stages (i.e, Diels–Alder reaction). We recognized that oxidation at C(3) of the aromatized model system would permit the synthesis of the jatropholones; however, such a reaction could be problematic in terms of regioselectivity [i.e., oxidation at C(1) vs. C(3)]. It was our intent to demonstrate first the feasibility of the Diels–Alder reaction with furan **12** and then to incorporate the requisite oxygen substituent as in furan **11**, thereby providing a more convergent approach.



(v) Synthesis of Furan 12: A Most Valuable Model System. We began the synthesis of furan **12** with the pyrrolidine enamine of cyclopentanone.[16] Acylation with *O*-acetoxylactoyl chloride[17] in benzene in the presence of triethylamine, followed by hydrolysis of the resultant enamine **13** and removal of the acetate group (KOH/MeOH or H_2SO_4/THF), led to hydroxy ketone **15**. *p*-Toluenesulfonic acid induced cyclodehydration in benzene with Dean-Stark removal of water then afforded furanone **16**. That **16** had been formed was suggested by strong IR absorption bands at 1700 and 1610 cm^{-1}, characteristic of 3(2*H*)-furanones.[18] Additional support was provided by the ^1H and ^{13}C NMR spectra.[18] O-Methylation of the lithium enolate prepared with LDA in THF containing HMPA (3 equiv) with dimethyl sulfate then provided furan **12** in five steps and 57% overall yield.

(vi) The Diels–Alder Reaction Revised: Application of High Pressure. Initial efforts to effect the requisite Diels–Alder reaction between furan **12** and enone **6** employing either thermal or Lewis acid[19] conditions again proved unsuccessful. The problem in this case appeared to lie with the instability of the diene component. In evidence here, we note that a dilute solution of furan **12** in $CDCl_3$ decomposes over a period of 24 h to give, in a relatively clean fashion, a more polar product whose structure was tentatively assigned as vinylogous ester **17** on the basis of spectral and elemental composition data, in conjunction with the known propensity of furans to undergo oxidation.[20] Particularly diagnostic were two methyl singlets at δ 2.44 and 3.75, as well as the absence of vinyl protons in the ^1H NMR spectrum and the presence of strong

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(11) (a) Corey, E. J.; Crouse, D. *J. Org. Chem.* **1968**, *33*, 298. (b) Corey, E. J.; Seebach, D. *J. Org.* Chem. **1975**, *40*, 231.
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(13) Evans, D. A. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, p 2.
(14) In the case at hand, the configuration of the silyl enol ether was not determined.
(15) For a review on this subject see: Wong, H. N. C.; Ng, T. K.; Wong, T. Y.; Xing, Y. D. *Heterocycles* **1984**, *22*, 875.
(16) Available from Aldrich; see also: Stork, G.; Brizzolaro, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207.
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(19) Brion, F. *Tetrahedron Lett.* **1982**, *23*, 5299.
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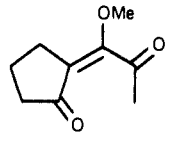
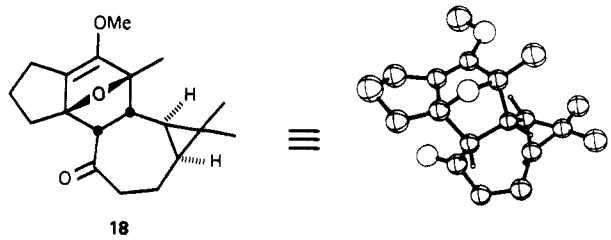


17

IR stretches at 1710 and 1605 cm^{-1}. In addition, a molecular ion at m/e 168 was observed in the mass spectrum.

Given our inability to effect the thermally induced cycloaddition, we turned to the use of high pressure. Furan cycloadditions[21] provide just one example of reactions available to the synthetic chemist which have a negative volume of activation and therefore can be accelerated by application of pressure (ca. 3–15 kbar).[22] Other examples include 1,3-dipolar cycloadditions,[23] Michael[24] and aldol reactions,[25] introduction of protecting groups,[26] and formation of Wittig reagents.[27] The high-pressure technique is particularly rewarding in the case of furan cycloadditions, due to the commonly encountered lack of stability of furans and their cycloadducts to elevated temperatures and Lewis acids.[15]

In the case at hand, application of 5 kbar of pressure[28] to a neat 1:1 mixture of **6** and **12** for 72 h afforded crystalline **18**. The yield was 80%! Recrystallization from pentane afforded crystals (mp 48–50 °C dec) suitable for X-ray analysis. Completion of the latter confirmed that the product was indeed the Diels–Alder adduct **18**, possessing the desired regiochemistry of the jatropholone skeleton.[29] Further examination of the ORTEP plot indicated that cycloaddition had occurred in an endo fashion.



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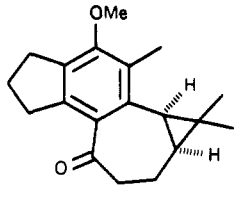
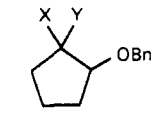


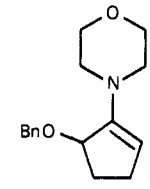
19

Aromatization of the oxabicyclo[2.2.1]heptene system proved quite facile. In particular, treatment of **18** with either acetic acid in chloroform or silica gel in chloroform afforded anisole **19** in near quantitative yield.

(vii) Preparation and Reaction of Furan 11: A More Convergent Approach. Given our success with the model furan, we turned to the preparation of the oxygen-substituted derivative **11**. This synthesis began with an acid-catalyzed ring opening of cyclopentene oxide in benzyl alcohol. Swern oxidation[30] of the resultant α-(benzyloxy)cyclopentanol (**20**) provided α-(benzyloxy)cyclopentanone (**21**).



20 X = OH, Y = H
21 X, Y = O



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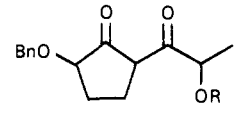
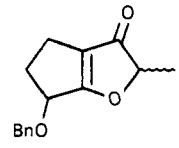


23 R = Ac
24 R = H

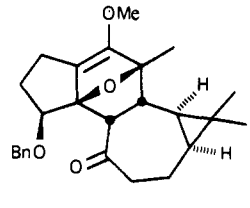


25

We were now faced with a regiochemical problem, namely formation of the less-substituted enamine. Not surprisingly, formation of either the pyrrolidine or piperidine enamine, employing standard benzene–*p*-TsOH conditions (Dean-Stark water removal), led to a mixture of regiochemical products. However, when morpholine was stirred with ketone **21** in ether in the presence of magnesium sulfate as a dehydrating agent, the less-substituted morpholine enamine **22** proved to be the exclusive regiochemical product. Acylation of the latter with *O*-acetoxyactoyl chloride,[17] followed by hydrolysis of the enamine and removal of the acetate group, as with the model system, proceeded without event to afford hydroxy diketone **24** in 47% yield for the three steps.

At this point, the marked difference in reactivity between the model and benzyloxy-substituted systems first became apparent. For example, attempted cyclodehydration employing the model system conditions resulted only in decomposition of **24**. After considerable experimentation, it was discovered that careful treatment with thionyl chloride in methylene chloride/pyridine, first at −78 °C for 5 min and then at 0 °C for 1 h, afforded furanone **25** in 52% yield as a 1:1 mixture of diastereomers. O-Methylation of this mixture also proved considerably more troublesome than in the unsubstituted system. Here, a variety of attempts to alkylate the lithium enolate went without success. The reaction was eventually found to proceed cleanly via the potassium enolate, formed by treatment of **25** with potassium hydride in THF containing 2 mol equiv HMPA. Alkylation with dimethyl sulfate under these rather precise conditions provided furan **11**. The overall yield for the eight-step sequence was 22%.

(viii) Preparation of Jatropholone A and B Acetates: A Marginal Success. With furan **11** in hand, we proceeded with the Diels–Alder reaction. Surprisingly, furan **11** was markedly less reactive, with only 2.4% of adduct **26** being formed after 4 days at 5 kbar.



26

(21) (a) Dauben, W. G.; Krabbenhoft, H. O. *J. Am. Chem. Soc.* **1976**, *98*, 1992. (b) Dauben, W. G.; Kessel, C. R.; Takemura, K. H. *J. Am. Chem. Soc.* **1980**, *102*, 6893. (c) De Shong, P.; Lowmaster, N. E. *Synth. Commun.* **1983**, *13*, 537. (d) Kotsuki, H.; Nishizawa, H. *Heterocycles* **1981**, *16*, 1287. (e) Jurczak, J.; Kozluk, T.; Filipek, S.; Eugster, C. H. *Helv. Chim. Acta* **1983**, *66*, 222.

(22) For a review of some organic reactions performed at high pressure, see: Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* **1985**, 1.

(23) Dicken, C. M.; De Shong, P. *J. Org. Chem.* **1982**, *47*, 2047.

(24) Bunce, R. A.; Schlecht, M. F.; Dauben, W. G.; Heathcock, C. W. *Tetrahedron Lett.* **1983**, *24*, 4943.

(25) Tomamoto, Y.; Maruyama, K.; Matsumoto, K. *J. Am. Chem. Soc.* **1983**, *105*, 6963.

(26) Dauben, W. G; Bunce, R. A.; Gerdes, J. M.; Heneger, K. E.; Cummingham, A. F., Jr.; Ottoboni, T. B. *Tetrahedron Lett.* **1983**, *24*, 5709.

(27) Dauben, W. G.; Gerdes, J. M.; Bunce, R. A. *J. Org. Chem.* **1984**, *49*, 4293.

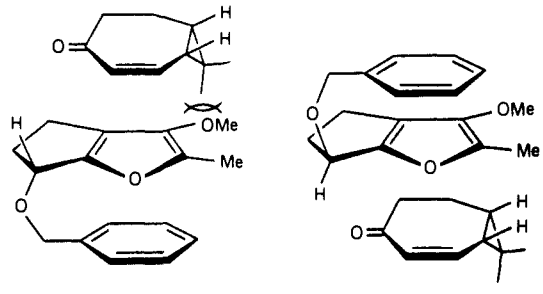
(28) The pressure apparatus used was identical with that designed by Prof. P. DeShong in Collaboration with LECO Corp., Tem-Press Div. (Bellefonte, PA); see: DeShong, P.; Dicken, C. M.; Perez, J. J.; Shoff, R. M. *Org. Prep. Proced. Int.*, **1982**, *14*, 369.

(29) Carroll, P., University of Pennsylvania, X-Ray Crystallographic Faculty, unpublished results.

(30) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

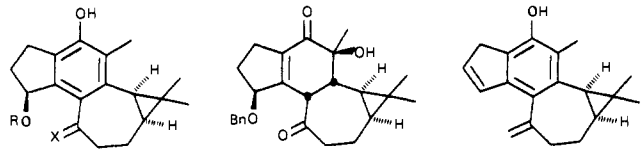
Increasing the pressure to 7 kbar and the reaction time to 14 days improved the yield, albeit only to 19%. Presumably the lower reactivity of furan **11** is due to a combination of electronic withdrawing effects and the steric encumbrance provided by the α-benzyloxy substituent. It seemed likely from available precedent that increasing the pressure to 15 or 20 kbar would have given further improvement in the yield.[22] However, due to the pressure limitation of the LECO Corporation high-pressure apparatus,[28] this was not investigated.

At this point, we should note that at both pressures studied, *a single diastereomer resulted* (i.e., <2% of the alternative diastereomer). This observation suggests that a kinetic resolution occurs during the cycloaddition. Such a result could arise via shielding of one face of the diene by π-stacking of the furan and benzene rings.[31] Such π-stacking would disfavor one of the two endo transition states (i.e., A), when reacting with homochiral enone **6**, containing the sterically demanding dimethylcyclopropyl group. On this basis and in analogy with the model system, the stereochemistry of **26** was assigned as indicated.



A B

Attempts to effect aromatization of **26** again demonstrated the great difference in the chemical behavior between the model and benzyloxy-substituted systems. A wide variety of conditions (including silica gel, acetic acid, TsOH, sodium hydride, tin tetrachloride, sodium ethoxide, and TMSI) resulted only in decomposition of the adduct. Eventually, a two-step protocol was developed which gave access to phenol **27**. The specific conditions consisted of initial brief treatment with boron trifluoride etherate in ether, buffered with sodium acetate, to give **28**. Not surprisingly, enone **28** proved to be an extremely sensitive compound. Fortunately, treatment of this material without purification with thionyl chloride in pyridine led to the rapid and efficient (82%) elimination of the tertiary hydroxyl group to give **27**. Methylenation of the resultant ketone with methylenetriphenylphosphorane then proceeded cleanly, albeit extremely slowly, even when a large excess was employed. Presumably the lack of reactivity in this case results from the deactivating effect of the *p*-phenoxide substituent, in conjunction with steric hinderance around the carbonyl.

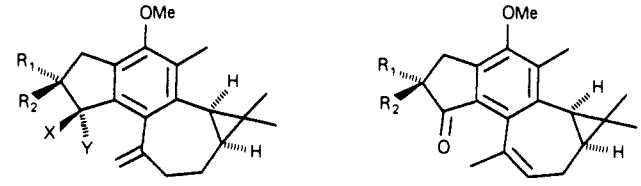


27 X = O, R = Bn
29 X = CH_2, R = Bn
31 X = CH_2, R = H

28 30

With elaboration of the tetracyclic system completed, we were now faced with removal of the benzyl group from **29**. *This transformation proved troublesome in the extreme!* A wide variety of conditions known to effect benzyl group removal[32] provided none of the desired product. This problem was not entirely unexpected in view of the doubly benzylic nature of the ether oxygen. Indeed, one could anticipate that either hydrogenolysis or Lewis acid-catalyzed cleavage would result in formation of the undesired *secondary* benzyl radical and/or cation, rather than the desired *primary* intermediate. With these possibilities in mind, we reasoned that a combination of a mild Lewis acid with a powerful nucleophile (known to cleave benzyl ethers)[33] would lead to nucleophilic attack at the less hindered of the two benzylic centers. Treatment of **29** with boron trifluoride etherate in ether containing ethanethiol led only to formation of indene **30**. Presumably the desired alcohol **31** was formed but proved sufficiently acid sensitive that elimination occurred under the reaction conditions. In an attempt to avoid elimination, the reaction was repeated with a large excess of anhydrous sodium acetate. These conditions, while providing the desired alcohol **31** in 61% yield, proved capricious on a number of occasions.

Undaunted, selective protection of the phenolic hydroxyl group as the methyl ether **32**, employing potassium carbonate and methyl iodide in acetone, followed by oxidation of the benzylic hydroxyl with PDC[34] afforded ketone **33**. The yield for the two steps was 74%. Alkylation of the LDA-derived lithium enolate at 0 °C with methyl iodide then yielded a mixture of jatropholone A and B methyl ethers (**34** and **35**), which in turn could be deprotected with sodium ethanethiolate in DMF at 100 °C for 18 h[35] to provide jatropholones A and B, although not in a very satisfactory manner (vide infra).



32 X = OH, Y = H, R_1 = R_2 = H
33 X, Y = O, R_1 = R_2 = H
34 X, Y = O, R_1 = H, R_2 = Me
35 X, Y = O, R_1 = Me, R_2 = H

36 R_1 = H, R_2 = Me
37 R_1 = Me, R_2 = H

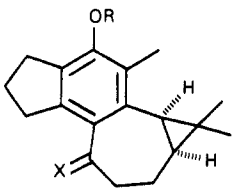
At this point in time, our only authentic sample for comparison purposes was jatropholone B acetate.[36] For this reason, we acetylated the demethylated material. The result, after careful separation and purification, was jatropholone B acetate, identical with the authentic sample, as well as jatropholone A acetate and the corresponding two endocyclic compounds **36** and **37**, the latter presumably arising during the demethylation.

While we had in fact completed a total synthesis of the jatropholones, we were not unconcerned with the awkward nature of the synthetic route, as well as the poor yield in the Diels–Alder reaction. Although we considered several new strategies, which would entail refinements in our choice of protecting groups, we chose instead to explore the regioselective oxidation of the considerably more available Diels–Alder adduct **19**. Our hope here was to uncover a more efficient approach.

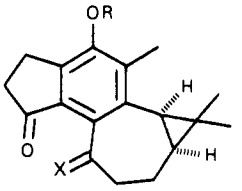
(ix) Return to the Model System: An Efficient Synthesis of Jatropholones A and B. The major obstacle in any attempt to introduce oxygen at C(3) in **19** was the presence of no less than four benzylic centers and one allylic (α to carbonyl) center, which could give rise to a large range of possible products. Our first and somewhat encouraging observation was obtained upon oxidation of **19** with the reagent derived from chromium trioxide and 3,5-dimethylpyrazole.[37] The result was a 47:53 mixture of regioisomeric diketones **38** and **39**, in a combined yield of 68%.

Structure assignments for **38** and **39**, initially based on spectral and elemental composition data, were strongly supported by conversion of **38** and **39** to corresponding phenols **40** and **41**, by

(31) Trost, B. M.; O'Krongly, D.; Beletine, J. L. *J. Am. Chem. Soc.* **1980**, *102*, 7595.
(32) For a review on the subject see: Bhatt, M. V.; Kulkarni, S. V. *Synthesis* **1983**, 249.
(33) (a) Fuji, K.; Ichikawa, K.; Node, M.; Fujita, E. *J. Org. Chem.* **1979**, *44*, 1661. (b) Node, M.; Hori, H.; Fujita, E. *J. Chem. Soc., Perkins Trans. 1* **1976**, 2737.
(34) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2644.
(35) Feutrill, G. I.; Mirrington, R. N. *Aust. J. Chem.* **1972**, *25*, 1719.
(36) We thank Prof. Connolly for an authentic sample of jatropholone B acetate.
(37) Salmond, W. G.; Barta, M. A.; Halvens, J. L. *J. Org. Chem.* **1978**, *43*, 2057.

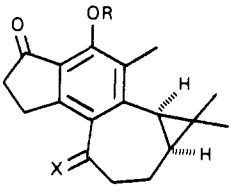


42 X = O, R = H
43 X = CH_2, R = H
44 X = O, R = TES
47 X = CH_2, R = TES



38 X = O, R = Me
40 X = O, R = H

45 X = O, R = TES
48 X = CH_2, R = TES



39 X = O, R = Me
41 X = O, R = H

46 X = O, R = TES
49 X = CH_2, R = TES

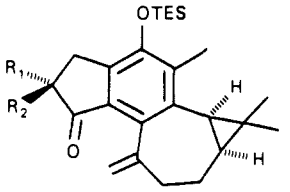
treatment with sodium cyanide in Me_2SO at 175 °C.[38] Infrared dilution studies in turn indicated the presence of an intramolecular hydrogen bond only in the case of **41**.

Having demonstrated that oxidation at other benzylic or allylic sites would not pose significant problems, we reasoned that the C(3) selectivity might be improved by employing a bulky protecting group on the phenolic hydroxyl. Toward this end, anisole **19** was treated with sodium cyanide in Me_2SO at 175 °C for 5 h to afford the corresponding phenol **42**, which was protected as the triethylsilyl ether[39] **44**. As anticipated, oxidation led to a 2:1 mixture of diketones **45** and **46**.

At this point, it also seemed plausible (we are optimists) that the ratio might be even further improved by carrying out the oxidation on olefin **47**, although the addition of yet another potentially oxidizable allylic position could complicate the situation. The presence of the exo-methylene olefin in **47** would, of course, be a major advantage in that differentiation between the C(3) and C(6) carbonyl groups later in the sequence could be avoided.

During the preparation of ample quantities of Diels–Alder adduct **18**, we discovered that **18** could be converted directly to phenol **42** by treatment with dilute hydrochloric acid in THF. The Wittig reaction with methylenetriphenylphosphorane followed by protection of the phenol as the triethylsilyl ether then gave **47**. The overall yield for this sequence was 57%. The regioselectivity in the oxidation step also improved to 6:1, although the yield of ketone **48** after purification by flash column chromatography was consistently 34%.

From this point forward, the synthesis proved free of major obstacles. The desired regioisomer **48**, separable from **49** by flash column chromatography, was methylated to provide a 24:76 mixture of jatropholones A and B protected as their TES ethers (i.e., **50** and **51**). These in turn were readily separated by HPLC. Deprotection via treatment with tetra-*n*-butylammonium fluoride[40] then proceeded without epimerization or olefin migration. That in fact (+)-jatropholones A and B (**1** and **2**) were in hand was demonstrated by careful comparison of their spectral (250-MHz



50 R_1 = H, R_2 = Me
51 R_1 = Me, R_2 = H

^1H NMR, ^{13}C NMR, IR, UV, MS, and optical rotation)[41] and physical (melting point) properties with those derived from now available authentic samples of (+)-jatropholones A and B.[42]

Summary. The first total synthesis of (+)-jatropholones A and B has been achieved. The synthetic route, which proved convergent (12 steps), relatively efficient (6%), and provided the jatropholones in homochiral form, served to establish for the first time the absolute stereochemistry as 9*S*,11*R*. Furthermore, the synthesis demonstrates that high pressure is a valuable technique in that its availability permits the design of synthetic strategies previously not feasible. Only slightly disappointing was the yield of benzylic oxidation. However, such oxidations can be a valuable protocol, even with the presence of several potential sites of oxidation.

Experimental Section

Materials and Methods. *n*-Butyllithium was standardized by titration with diphenylacetic acid.[42] Analytical TLC was carried out with precoated 0.25 mm thickness silica gel plates with fluorescent indicator (E. Merck). The high-pressure apparatus used was identical with that designed by Prof. P. DeShong in collaboration with the LECO Corp., Tem-Press Division (Bellefonte, PA) and described previously.[28]

Dithiane 9. To a stirred solution of 2-ethyl-1,3-dithiane (7.56 g, 48 mmol) in dry THF (125 mL) at −40 °C under argon was added *n*-butyllithium (46.1 mmol). After 4 h, 2-cyclopentenone (2.55 mL, 30.4 mmol) in 30 mL of THF was added dropwise over 10 min. The solution was gradually warmed to 0 °C, and after 1 h, 25 mL of water was added along with saturated aqueous sodium bicarbonate solution (50 mL). The phases were separated and the aqueous phase extracted with ether. The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Excess 2-ethyl-1,3-dithiane was removed by Kugelrohr distillation (90 °C, 1 mmHg) to afford 4.37 g (63%) of dithiane **9** which was used without further purification: NMR (60 MHz, CCl_4) δ 5.89 (br s, 2 H), 3.37–1.55 (m, 13 H), 1.15 (t, *J* = 7 Hz, 3 H).

Diketo Alcohol 15. To a stirred solution of acetate **14** (4.15 g, 20.9 mmol) in THF (50 mL) was added 3 N sulfuric acid (100 mL). The resultant mixture was stirred for 48 h at room temperature before addition to chloroform (100 mL). The phases were separated and the aqueous phase extracted with chloroform. The combined extracts were dried ($MgSO_4$), and the sovlent was removed in vacuo to give 3.14 g (96%) of alcohol **15**: IR ($CHCl_3$) 3700–2400 (br s), 1750–1680 (s), 1600 (m), 1450 (m) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 4.78 (br s, 2 H), 4.26 (q, *J* = 7 Hz, 1 H), 2.70–1.70 (m, 6 H), 1.40 (d, *J* = 7 Hz, 3 H); electron impact mass spectrum, *m/e* 156.0792 (M^+, calcd for $C_8H_{12}O_3$, 156.0786).

Hydroxy Ketone 4. To a stirred solution of dithianyl alcohol **9** (4.00 g, 17.2 mmol) in 250 mL of dioxane at room temperature was added 250 mL of 1% aqueous sulfuric acid. After 4 h, the reaction mixture was extracted with ether. The combined organic phases were washed with saturated sodium bicarbonate solution, water, and brine and dried ($MgSO_4$), and the solvent was removed in vacuo to afford 2.61 g (66%) of the rearranged dithianyl alcohol **10**: NMR (60 MHz, $CDCl_3$) δ 6.0 (m, 1 H), 4.9 (m, 1 H), 2.9–1.6 (m, 13 H), 0.80 (t, *J* = 7 Hz, 3 H). A solution of **10** (2.61 g, 11.2 mmol) in aqueous acetonitrile (125 mL, 8:2 acetonitrile/water) was added to calcium carbonate (2.26 g, 23.6 mmol) and mercuric chloride (6.52 g, 24.0 mmol) under nitrogen. The mixture was heated to 50 °C for 5 h, cooled, and filtered and the solid residue washed several times with benzene. The filtrate and washings were washed with water and brine and dried ($MgSO_4$), and the solvent was

(38) McCarthy, J. R.; Moore, J. L.; Gregge, R. J. *Tetrahedron Lett.* **1978**, 5183.
(39) (a) Hart, T. W.; Metcalfe, D. A.; Scheinmann, F. *J. Chem. Soc., Chem. Commun.* **1979**, 156. (b) Koft, E. R.; Smith, A. B., III. *J. Am. Chem. Soc.* **1982**, *104*, 2659.
(40) Corey, E. J.; Snider, B. B. *J. Am. Chem. Soc.* **1972**, *94*, 2549.
(41) Rotations for the natural jatropholones have not previously been reported; natural material was therefore separated by HPLC and the rotations were determined. It should be noted that in the preliminary communication,[6] the rotations were transposed and should read jatropholone A, $[\alpha]^{20}_D$ +107.2° (*c* 0.070, $CHCl_3$); jatropholone B, $[\alpha]^{20}_D$ +80.3° (*c* 0.128, $CHCl_3$).
(42) We thank Prof. Connolly (University of Glasgow) for the authentic spectra and generous samples of jatropholones A and B.
(43) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.
(44) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *42*, 2923.

removed in vacuo to afford the crude product. Purification by flash column chromatography (50% ethyl acetate/hexane) gave 665 mg (42%) of hydroxy ketone **4**: IR (CCl_4) 3400 (br m), 1650 (s) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 6.66 (m, 1 H), 5.04 (m, 1 H), 3.36 (br s, 1 H), 2.74 (q, J = 7.4 Hz, 2 H), 2.68 (m, 1 H), 2.40 (m, 2 H), 1.78 (m, 1 H), 1.10 (t, J = 7 Hz, 3 H); electron impact mass spectrum, m/e 140.0838 (M^+ calcd for $C_8H_{12}O_2$, 140.0837).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.62. Found: C, 68.48; H, 8.62.

Diketoacetate 14. To a stirred of 1-pyrrolidinocyclopentene (15.5 g, 113 mmol) and dry triethylamine (17.3 mL, 124 mmol) in dry benzene (250 mL) under argon was added acid chloride **2** (15.5 g, 103 mmol) in 10 mL of dry benzene. The reaction mixture was then heated at reflux for 8 h, cooled to room temperature, and filtered through Celite. The filtrate was evaporated in vacuo to give the acylated enamine **13** which was used without further purification: NMR (250 MHz, $CDCl_3$) δ 5.28 (q, J = 7 Hz, 1 H), 3.55 (m, 2 H), 3.12 (m, 2 H), 3.0–2.5 (m, 4 H), 2.10 (s, 3 H), 2.0–1.6 (m, 6 H), 1.34 (d, J = 7 Hz, 3 H). The above enamine was dissolved in water (75 mL), acetic acid (75 mL), and THF (150 mL) and the resultant dark-brown solution stirred at room temperature for 48 h. The reaction mixture was then added to water (200 mL) and chloroform (200 mL), the phases were separated, and the aqueous phase was extracted with chloroform. The combined organic extracts were dried ($MgSO_4$), and the solvent was removed in vacuo to give a residue which was purified by flash column chromatography (20–25% ethyl acetate/hexane) to give 15.I g (68%) of diketoacetate **14** as a pale-yellow oil: IR (neat) 3450 (m), 2950 (s), 1730 (s), 1640 (s), 1235 (s); NMR (250 MHz, $CDCl_3$) δ 8.80 (br s, 0.17 H, enol OH), 5.27, 5.20 (2q, J = 7 Hz, 1 H), 3.75, 3.46 (2t, J = 7.5 Hz, 0.83 H, keto form), 2.90–1.8 (m, 9 H), 1.45 (3d, J = 7 Hz, 3 H); electron impact mass spectrum, m/e 198.0907 (M^+, calcd for $C_{10}H_{14}O_4$ 198.0892).

Furanone 16. A solution of *p*-TsOH (200 mg) in benzene (150 mL) was dried azeotropically. Alcohol **4** (3.13 g, 20.1 mmol) was then added and the mixture heated at reflux with Dean-Stark removal of water. After 8 h, the solution was cooled and poured into brine, the organic layer separated, and the aqueous layer extracted with ether. The combined extracts were dried ($MgSO_4$), and the solvent was removed in vacuo to afford, after flash column chromatography (50% ethyl acetate/hexane), 2.40 g (87%) of pure furanone **16**: IR ($CHCl_3$) 1700 (s), 1610 (s), 1450 (m), 1225 (m), 1050 (m) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 4.95 (q, J = 7.2 Hz, 1 H), 2.58 (m, 2 H), 2.39 (m, 4 H), 1.52 (d, J = 7.2 Hz, 3 H); ^{13}C NMR δ 198.3 (s), 196.0 (s), 118.2 (s), 91.5 (d), 26.3 (t), 24.9 (t), 20.1 (t), 15.7 (q); electron impact mass spectrum, m/e 138.0673 (M^+, calcd for $C_8H_{10}O_2$, 138.0681).

Furan 12. To a stirred solution of diisopropylamine (0.6 mL, 4.28 mmol) in dry THF (50 mL) at 0 °C under argon was added *n*-butyllithium (2.75 mL, 1.44 M, 3.96 mmol). After 15 min, a solution of the furanone **16** (500 mg, 3.62 mmol) in dry THF (3 mL) was added dropwise. The solution was stirred for 1 h while warming to room temperature. Dry hexamethylphosphoramide (2 mL, 11.5 mmol) was added, followed by dimethyl sulfate (0.40 mL, 4.22 mmol). After the solution was stirred for an additional 1 h, ammonium hydroxide solution (14 M, 20 mL) was added and the stirring continued for 45 min. The mixture was then poured into water (100 mL) and ether (50 mL), and the phases were separated. The aqueous phase was extracted with ether, the combined extracts were washed with water and brine and dried ($MgSO_4$), and the solvent was removed in vacuo to give 540 mg (98%) of furan **12**: IR (CCl_4) 3000–2900 (m), 1640 (w), 1450 (m), 1340 (m), 1175 (m) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 3.70 (s, 3 H), 2.70–2.50 (m, 4 H), 2.35 (m, 2 H), 2.14 (s, 3 H); electron impact mass spectrum, m/e 152.0840 (M^+, calcd for $C_9H_{12}O_2$, 152.0837).

Bicycloheptene 18. A homogeneous mixture of furan **12** (500 mg, 3.29 mmol) and (−)-8,8-dimethylbicyclo[5.1.0]oct-2-en-4-one (500 mg, 3.33 mmol) was placed in a disposable plastic syringe. The syringe was capped and placed in the LECO pressure vessel and the pressure raised to 5 kbar (71000 psi) and maintained at that pressure for 72 h. After depressurization, traces of starting materials were removed under high vacuum to afford 800 mg (81%) of Diels–Alder adduct **18**. A portion of this material was recrystallized (pentane) to yield crystals suitable for X-ray analysis: mp 48–50 °C dec; IR (CCl_4) 3000–2850 (m), 1700 (s), 1450 (m), 1275 (m), 1210 (m), 1110 (m), 1060 (m) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 3.75 (s, 3 H), 3.40 (d, J = 11 Hz, 1 H), 2.95–1.70 (m, 11 H), 1.39 (s, 3 H), 1.12 (s, 3 H), 1.00 (s, 3 H), 0.59 (m, 1 H), 0.25 (t, J = 9 Hz, 1 H); electron impact mass spectrum, m/e 302.1903 (M^+, calcd for $C_{19}H_{26}O_3$, 302.1882).

Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.50; H, 8.60. Found: C, 75.57; H, 8.67.

Ketone 19. To a stirred solution of Diels–Alder adduct **18** (101 mg, 0.334 mmol) in distilled chloroform (10 mL) was added glacial acetic acid (3 drops). The reaction was monitored by TLC which revealed the slow disappearance of the non-UV-active starting material with concomitant appearance of a lower R_f, UV-active spot (presumably the product of initial β-elimination of the bridgehead oxygen) and a higher R_f UV-active spot corresponding to the desired product. After 48 h, the lower R_f spot and starting material had all been consumed. The solvent was removed in vacuo to provide 90 mg (95%) of ketone **19** as a viscous oil which crystallized on standing. Recrystallization from hexane provided an analytical sample: mp 77–78 °C; $[\alpha]^{20}_D$ +111° (c 0.282, $CHCl_3$); UV λ_m (EtOH) 262, 223, 208 nm (ϵ_{max} 4500, 14 100, 14 400); IR ($CHCl_3$), 2950 (s), 1680 (s), 1580 (m), 1340 (m), 1290 (s), 1195 (m), 1160 (s), 1095 (m); NMR (250 MHz, $CDCl_3$) δ 3.80 (s, 3 H), 3.15–2.40 (m, 6 H), 2.18 (s, 3 H), 2.15–1.85 (m, 3 H), 1.60 (d, J = 10 Hz, 1 H), 1.40 (m, 1 H), 1.23 (s, 3 H), 1.12 (m, 1 H), 0.92 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 209.0 (s), 156.6 (s), 143.0 (s), 134.4 (s), 134.3 (s), 134.1 (s), 129.8 (s), 59.1 (q), 43.0 (t), 32.2 (t), 30.2 (t), 28.8 (d), 28.4 (d), 25.2 (t), 20.9 (s), 20.0 (t), 15.7 (q), 12.5 (q); electron impact mass spectrum, m/e 284.1776 (M^+, calcd for $C_{19}H_{24}O_2$, 284.1776).

2-(Benzyloxy)cyclopentanol (20). To a mixture of commercial cyclopentene oxide (8.4 g, 0.1 mol) and benzyl alcohol (32.4 g, 0.3 mol), 4 drops of concentrated sulfuric acid were added with vigorous stirring. The mixture was slowly heated to 95 °C over a period of 45 min and maintained at that temperature for 1 h. The mixture was then cooled to room temperature, diluted with ether (500 mL), and washed with saturated sodium bicarbonate solution, water, and brine. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The excess benzyl alcohol was then removed by vacuum distillation. The residue was used in subsequent reactions without further purification; the yield of **20** was 18.6 g (97%). For characterization purposes, a pure sample of **20** was obtained by flash column chromatography (20% ether/hexane): IR (CCl_4) 3600 (w), 3450 (w), 2970 (s), 1090 (s), 690 (m) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 7.34 (s, 5 H), 4.55 (ABq, J_{ab} = 12.0 Hz, 2 H), 4.16 (m, 1 H), 3.76 (m, 1 H), 2.1–1.5 (m, 7 H); electron impact mass spectrum, m/e 192.1166 (M^+, calcd for $C_{12}H_{16}O_2$, 192.1149).

2-(Benzyloxy)cyclopentanone (21). To a flame dried 250-mL round-bottom flask was added under argon dry CH_2Cl_2 (70 mL) followed by freshly distilled oxalyl chloride (6.98 g, 0.55 mmol). The mixture was cooled to −78 °C and freshly distilled dimethyl sulfoxide (8.58 g, 0.11 mol) was added via cannula over a 2-min period. After an additional 2 min, a solution of alcohol **20** (9.6 g, 50 mmol) in CH_2Cl_2 (30 mL) was added over 3 min, and stirring continued at −78 °C for 15 min. Triethylamine (25.25 g, 0.25 mol) was then added in one portion and the mixture warmed to room temperature (ca. 1 h), quenched with water (100 mL), and extracted several times with ether. The combined organic extracts were washed with 5% sodium bicarbonate solution, water, and brine, dried ($MgSO_4$), and concentrated in vacuo. The resultant product was distilled under reduced pressure (1–2 mmHg) to yield 8.93 g (94%) of pure **21** (distillation temperature 105–108 °C): IR (CCl_4) 2970 (s), 1750 (s), 1115 (s), 690 (m), cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 7.35 (s, 5 H), 4.76 (ABq, J_{ab} = 11.0 Hz, 2 H), 3.80 (t, J = 9.0 Hz, 2 H); electron impact mass spectrum, m/e 190.1058 (M^+, calcd for $C_{12}H_{14}O_2$, 190.0933).

Diketoacetate 23. A solution of the ketone **21** (14.18 g, 75 mmol) and morpholine (13.0 g, 150 mmol) in dry ether (200 mL) was stirred with magnesium sulfate (32 g) for 48 h. At that time, the IR spectrum of an aliquot indicated the absence of any carbonyl functionality. The mixture was then diluted with ether, filtered, and concentrated in vacuo to yield 19.3 g (~100%) of enamine **22**. This product was used without purification: IR (CCl_4) 2960 (s), 2850 (s), 1630 (m), 1120 (s) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 7.34 (s, 5 H), 4.88–4.32 (m, 4 H), 3.94–3.54 (m, 4 H), 3.14–2.74 (m, 4 H), 2.54–1.50 (m, 4 H).

To a solution of enamine **22** (19.4 g, 75 mmol) in dry benzene (400 mL) was added freshly distilled triethylamine (11.46 mL, 82 mmol), and the mixture was heated to reflux. A solution of acetoxylactoyl chloride (11.85 g, 79 mmol) in dry benzene (100 mL) was then added dropwise over a 30-min period. The mixture was then heated at reflux for a further 6 h, cooled to room temperature, and filtered and the residue washed with dry ether. The combined filtrates were concentrated in vacuo to yield 26.3 g (~95%) of acylenamine. The material thus obtained was dissolved in THF (250 mL) to which water (25 mL) and glacial acetic acid (25 mL) were added. The resultant solution was then stirred under argon at room temperature for 18 h. A mixture of CH_2Cl_2–ether (3:1, 500 mL) was added, and the organic extracts were washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was subjected to flash column chromatography (10% ethyl acetate/hexane) to afford 1.73 g of ketone **21** followed by 10.62 g of diketoacetate **23** (47.8% yield for three steps): IR (CCl_4) 2940 (m), 2870 (m), 1740 (s), 690 (m) cm^{-1}; NMR ($CDCl_3$) δ 7.34 (s, 5 H), 5.20 (m, 1 H), 4.76 (m, 2 H), 4.33 (t, J = 9 Hz, 1 H), 2.8–2.1 (m, 3 H), 2.12 (s, 3 H), 2.0–1.8 (m, 2 H), 1.43 (dd, J = 9 Hz, 3 H); electron impact mass spectrum, m/e 304.1376 (M^+, calcd for $C_{17}H_{20}O_5$, 304.1309).

Furanone 25. To a stirred solution of the diketoacetate **23** (3.04 g, 10 mmol) in methanol (22.8 mL) and pyridine (7.6 mL) was added 7.6 mL of 2 N potassium hydroxide solution. After 30 min at room temperature, CH_2Cl_2–ether (1:3; 300 mL) was added. The organic phase was washed with 5% citric acid solution and water, dried ($MgSO_4$), and concentrated in vacuo to yield 2.6 g (~100%) of hydroxy ketone **24**, which was used for the next reaction without purification: IR ($CHCl_3$) 3490 (w), 2940 (m), 1750 (s), 1110 (m), 700 (m) cm^{-1}.

A solution of hydroxy ketone **24** (2.6 g, 10 mmol) in dry CH_2Cl_2 (23 mL) and pyridine (11.5 mL) was cooled to −78 °C under argon. Thionyl chloride (2.15 mL, 30 mmol) was then added dropwise over a 5-min period. After an additional 10 min, the dry ice–acetone bath was replaced with an ice bath and the mixture stirred for 1 h while warming slowly to room temperature. Ether was then added and the mixture poured into 5% sodium bicarbonate solution. The organic phase was washed with 5% sodium bicarbonate solution and water, dried, ($MgSO_4$) and concentrated in vacuo. The residue was subjected to flash chromatography (15% ethyl acetate–hexane) to yield 1.27 g (52% for two steps) of furanone **25**: IR ($CHCl_3$) 3000 (m), 1685 (s), 1600 (s), 1100 (m), 695 (m) cm^{-1}; NMR ($CDCl_3$) δ 7.36 (s, 5 H), 5.00 (q, J = 9 Hz, 1 H), 4.86–4.56 (m, 3 H), 2.78–2.18 (m, 4 H), 1.58, 1.56 (dd, J = 9 Hz, 3 H); electron impact mass spectrum, m/e 244.1100 (M^+, calcd for $C_{15}H_{16}O_3$, 244.1099).

Furan 11. In a flame-dried 50-mL three-neck round-bottom flask, potassium hydride [2.88 g, 35% dispersion in oil (1.01 g, 25 mmol)] was washed under argon with dry ether (4 × 10 mL). The residual ether was removed with a stream of argon and dry tetrahydrofuran (20 mL) added. The mixture was cooled to 0 °C and a solution of furanone **25** (2.07 g, 8.5 mmol) in tetrahydrofuran (10 mL) and HMPA (3 mL) was added, followed immediately by dimethyl sulfate (2.36 mL, 25 mmol). The yellow solution was stirred in an ice bath for 3 h. Ammonium hydroxide (7 mL, 14 N) was added and the mixture stirred for 15 min and then diluted with ether (300 mL). The organic phase was washed with saturated ammonium chloride solution and water, dried ($MgSO_4$), and concentrated in vacuo to yield 2.13 g (97.7%) of furan **11**, which was used without purification. This compound undergoes considerable decomposition at room temperature and thus is best prepared immediately prior to use: IR (CCl_4) 3000 (m), 2940 (s), 1630 (m), 700 (m) cm^{-1}; NMR ($CDCl_3$) δ 7.36 (s, 5 H), 4.78 (br s, 1 H), 4.64 (ABq, J_{ab} = 12 Hz, 2 H), 3.68 (s, 3 H), 2.96–2.30 (m, 4 H), 2.18 (s, 3 H); electron impact mass spectrum, m/e 258.1251 (M^+, calcd for $C_{16}H_{18}O_3$, 258.1255).

Diels–Alder Adduct 26. A mixture of furan **11** (2.59 g, 10 mmol) and (−)-8,8-dimethylbicyclo[5.1.0]oct-2-en-4-one (6) (1.50 g, 10 mmol) was taken up in a 5.0-mL disposable plastic syringe (Aldrich). The syringe was then sealed and placed in the LECO high-pressure reactor. The presusre was raised to 6.87 kbar (96 200 psi) and held at that pressure for 300 h. The pressure was then released and the syringe removed and opened. The reaction mixture was subjected to flash column chromatography (10% ethyl acetate/hexane) to yield a mixture (2.11 g) of the unreacted furan **11** and enone 6 followed by the Diels–Alder adduct **26** (510 mg, 19%, 51% based on recovered enone) as a yellow oil: IR (CCl_4) 2940 (s), 1700 (s) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 7.32 (s, 5 H), 4.60 (ABq, 2 H), 3.96 (t, J = 9 Hz, 1 H), 3.75 (s, 3 H), 3.40 (d, J = 11 Hz, 1 H), 2.82–1.82 (m, 9 H), 1.44 (s, 3 H), 1.12 (s, 3 H), 1.00 (s, 3 H), 0.57 (m, 1 H), 0.24 (t, J = 9 Hz, 1 H); electron impact mass spectrum, m/e 408.2324 (M^+, calcd for $C_{26}H_{32}O_4$, 408.2292).

Ketone 27. To a solution of 74 mg (0.18 mmol) of adduct **26** in 25 mL of distilled ether was added 1.5 g of anhydrous sodium acetate. The mixture was stirred vigorously, while 0.25 mL (2.03 mmol) of boron trifluoride etherate (distilled) was added in one portion. After 5 min, the mixture was poured into water (25 mL) and extracted with ether, the combined organic extracts dried (K_2CO_3), and the solvent removed in vacuo. The acid-sensitive enone **28** thus obtained (65.5 mg, 92%) was used without further purification: IR (neat) 3600–3200 (m), 1710 (s), 1680 (s) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 7.34–7.29 (m, 5 H), 4.71 (t, J = 5 Hz, 1 H), 4.44 (center of AB, J = 11.7 Hz, 2 H), 4.02 (d, J = 8 Hz, 1 H), 3.57 (br s, 1 H), 2.8–0.8 (m, 11 H), 1.26 (s, 3 H), 1.11 (s, 3 H), 1.04 (s, 3 H).

Enone **28** (200 mg, 0.5 mmol) was dissolved in a mixture of 16 mL of dry pyridine and 125 mL of dry CH_2Cl_2 under nitrogen. The mixture was cooled to 0 °C and thionyl chloride (1.5 mL, 20.5 mmol) added dropwise. After addition was complete, the mixture was stirred at 0 °C for 15 min and then poured into ether. The organic phase was washed with saturated sodium bicarbonate and dried ($MgSO_4$) and the solvent removed in vacuo to afford a solid residue. Recrystallization gave 157 mg (82%) of ketone **27**: mp 151–154 °C; IR ($CHCl_3$) 3400 (m), 2950 (s), 1685 (s), 1280 (m), 1100 (s) cm^{-1}: NMR (250 MHz, $CDCl_3$) δ 7.33 (m, 5 H), 5.25 (t, J = 6 Hz, 1 H), 4.67 (br s, 1 H), 4.46 (center of AB, J = 10 Hz, 2 H), 3.0–2.35 (m, 5 H), 2.15 (s, 3 H), 2.10–1.8 (m, 2 H), 1.24 (s, 3 H), 1.2–0.9 (m, 2 H), 0.88 (s superimposed upon m, 4 H); electron impact mass spectrum, m/e 376.2198 (M^+, calcd for $C_{25}H_{28}O_3$, 376.2038.

Anal. Calcd for $C_{25}H_{28}O_3$: C, 79.75; H, 7.44. Found: C, 79.37; H, 7.45.

Anisole 32. In a flask fitted with a reflux condenser and nitrogen inlet, 3.5 g of methyltriphenylphosphonium bromide (9.8 mmol) was suspended in 50 mL of dry toluene. To this was added *n*-butyllithium (3.5 mL, 2.41 M, 8.4 mmol). The resulting deep-yellow suspension was stirred for 15 min to allow complete formation of the ylide; then a solution of 300 mg (0.8 mmol) of ketone **27** in 3 mL of dry THF was added and the solution heated at reflux with stirring. After 48 h, the reaction was judged complete as shown by TLC. The mixture was poured into water and extracted several times with ether, the combined organic phases were washed with brine and dried ($MgSO_4$), and the solvent was removed in vacuo. Flash column chromatography (25% ethyl acetate/hexane) gave 249 mg (83%) of pure olefin **29**: IR (neat) 3400 (m), 1585 (s), 1460 (s), 795 (m) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 7.33 (m, 5 H), 5.23 (m, 1 H), 5.08 (br s, 1 H), 4.75 (br s, 1 H), 4.47 (center of AB, J = 10 Hz, 2 H), 3.80 (br s, 1 H), 3.00 (m, 1 H), 2.82 (m, 1 H), 2.55 (m, 2 H), 2.19 (m, 1 H), 2.18 (s, 3 H), 1.73 (m, 1 H), 1.59 (m, 2 H), 1.26 (s, 3 H), 0.843 (s, superimposed on m, 5 H).

A solution of 250 mg (0.67 mmol) of olefin **29** in 10 mL of distilled ethanethiol was stirred while 6.0 g of anhydrous sodium acetate was added. The suspension was stirred vigorously at room temperature while 2.3 mL of boron trifluoride etherate (distilled from calcium hydride) was added in one portion. Rapid stirring was continued for 3 min. The mixture was then poured into saturated sodium bicarbonate solution and extracted with ether. The combined organic phases were dried (K_2CO_3). Removal of the solvent in vacuo gave 115.6 mg (61%) of alcohol **31** which was utilized without further purification.

To a solution of 100.0 mg (0.35 mmol) of alcohol **31** in 10 mL of dry acetone was added 1 g of anhydrous potassium carbonate followed by 1 mL (16.0 mmol) of methyl iodide. The reaction was stirred at room temperature and monitored by thin-layer chromatography. After 18 h (all starting material consumed), the mixture was filtered to remove solids and the solvent removed in vacuo to provide 99.7 mg (96%) of **32**: IR (neat) 3400 (w), 2930 (m), 1460 (w) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 5.42 (br t, 1 H), 5.22 (br s, 1 H), 4.88 (br s, 1 H), 3.80 (s, 3 H), 3.1–1.0 (m, 11 H), 2.23 (s, 3 H), 1.23 (s, 3 H), 0.86 (s, 3 H); chemical ionization mass spectrum, m/e 299.1952 (MH^+, calcd for $C_{20}H_{27}O_2$, 299.2012).

Ketone 33. To a solution of 90 mg (0.315 mmol) of alcohol **32** in 5 mL of dry CH_2Cl_2 was added 500 mg (0.95 mmol) of pyridinium dichromate in one portion. The mixture was stirred at room temperature, and after 15 min, the reaction was complete as judged by TLC. The mixture was then diluted with ether and filtered through a short pad of Florisil. The filtrate was concentrated in vacuo to give 69 mg (77.2%) of pure ketone **33**: IR (neat) 2920 (m), 1715 (s), 1460 (m) cm^{-1}; NMR ($CDCl_3$) δ 5.23 (br s, 1 H), 4.67 (br s, 1 H), 3.83 (s, 3 H), 3.06 (m, 2 H), 2.67 (m, 4 H), 2.28 (s, 3 H), 1.25 (s, 3 H), 0.81 (s, 3 H), 2.20–0.99 (m, 4 H); electron impact mass spectrum, m/e 296.1780 (M^+, calcd for $C_{20}H_{24}O_2$, 296.1776).

Methyl Ketone 35. To a solution of 26.2 mg (0.88 mmol) of ketone **33** in 5 mL of dry THF at 0 °C under nitrogen was added 0.18 mL of a 0.48 M standard solution of lithium diisopropylamide (0.86 mmol). The mixture was stirred at 0 °C for 30 min before the addition of 0.22 mL (0.35 mmol) of distilled methyl iodide. The reaction was allowed to warm slowly to room temperature; after 1 h, a mixture of starting material and mono- and dialkylated products was observed by TLC. The reaction was quenched with water, the mixture was extracted with ether, and the combined organic phases were dried ($MgSO_4$). Removal of solvent in vacuo and preparative thin-layer chromatography provided 13.0 mg (48%) of ketones **34** and **35** as a 1:2 mixture of diastereomers as judged by 250-MHz ^1H NMR integration: IR (neat) 2940 (s), 1715 (s), 1590 (w), 1470 (m), 1380 (m) cm^{-1}; NMR (major diastereomer, **35**) ($CDCl_3$) δ 5.24 (br s, 1 H), 4.68 (br s, 1 H), 3.84 (s, 3 H), 3.29 (AB, 3 H), 2.20–0.90 (m, 4 H), 1.24 (s, 3 H), 0.81 (s, 3 H); electron impact mass spectrum, m/e 310.1954 (M^+, calcd for $C_{21}H_{26}O_2$, 310.1933).

Jatropholone A and B Acetates.[36] To 2 mL of distilled ethanethiol and 2 mL of distilled dimethylformamide was added sodium hydride (0.24 g of an 80% dispersion in oil, 9.0 mmol) and the resultant mixtures stirred for 5 min at room temperature. To this, anisoles **34** and **35** (6.9 mg, 0.02 mmol) in 1 mL of ethanethiol were added, and the mixture was heated with stirring under N_2 to 100 °C for 18 h. At the end of this period, the mixture was cooled to room temperature, poured into water, and extracted with ether, the ether extracts were dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was then taken up in pyridine (3 mL) and acetic anhydride (1 mL) added. After 18 h, the volatiles were removed in vacuo, and the residue was subjected to preparative thin-layer chromatography (three developments, 10% ethyl acetate/hexane).

The first band contained only one stereoisomer of the endocyclic olefin. The second band contained a mixture of the other endocyclic olefin diastereomer and jatropholone A acetate. The third contained 1.3 mg of jatropholone B acetate:[36] NMR (250 MHz, $CDCl_3$) δ 5.26 (br s, 1 H), 4.73 (br s, 1 H), 3.12 (dd, J = 7, 16 Hz, 1 H), 2.75–2.4 (m, 4 H), 2.38 (s, 3 H), 2.17 (s, 3 H), 1.80 (m, 1 H), 1.56 (A, J = 9 Hz, 1 H) 1.27 (d, J = 7 Hz, 3 H), 1.23 (s, 3 H), 1.0–0.8 (m, 2 H), 0.81 (s, 3 H).

Diketones 38 and 39. To a stirred suspension of dry chromium trioxide (5.0 g, 50 mmol) in 65 mL of dry CH_2Cl_2 at −20 °C under argon was added 3,5-dimethylpyrazole (4.8 g, 50 mmol). The reagent was allowed to form over 15 min at −10 °C before the addition of ketone **19** (495 mg, 1.74 mmol) in 15 mL of dry CH_2Cl_2. The reaction mixture was then stirred at −20 °C for 14 h, poured into sodium hydroxide solution (150 mL, 2 M), and extracted several times with ether. The combined extracts were washed with water and brine and dried ($MgSO_4$), and the solvent was removed in vacuo. Purification by flash column chromatography (40% ethyl acetate/hexane) afforded 185 mg (36%) of diketone **39** as a colorless oil, followed by 165 mg (32%) of diketone **38**.

38: mp 173–174 °C; $[\alpha]^{20}_D$ +151° (c 0.515, $CHCl_3$); UV λ_{max} (EtOH) 295, 256, 212 nm (ϵ_{max} 1230, 5300, 15 500); IR ($CHCl_3$) 2950 (m), 1710 (s), 1590 (m), 1460 (m), 1370 (m), 1330 (m) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 3.84 (s, 3 H), 3.12 (m, 2 H), 2.92 (m, 2 H), 2.64 (m, 2 H), 2.26 (s, 3 H), 2.04 (m, 1 H), 1.63 (d, J = 7 Hz, 1 H), 1.45–1.05 (m, 2 H), 1.25 (s, 3 H), 0.86 (s, 3 H); electron impact mass spectrum, m/e 298.1561 (M^+, calcd for $C_{19}H_{22}O_3$, 298.1568).

39: $[\alpha]^{20}_D$ +112° (c 1.70, $CHCl_3$); IR ($CHCl_3$) 2940 (m), 1705 (vs), 1680 (s), 1575 (s), 1305 (m), 1280 (m) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 3.94 (s, 3 H), 3.27 (m, 1 H), 2.90–2.55 (m, 5 H), 2.21 (s, 3 H), 2.05 (m, 1 H), 1.56 (d, J = 7 H, 1 H), 1.4–1.0 (m, 2 H), 1.29 (s, 3 H), 0.91 (s, 3 H); electron impact mass spectrum, m/e 298.1575 (M^+, calcd for $C_{19}H_{22}O_3$, 298.1568).

Phenol 40. Caution: This reaction must be carried out in a well-ventilated hood. A solution of methyl ether **38** (43 mg, 0.14 mmol) in dry Me_2SO (3 mL) was degassed by passing argon through the solution for 10 min. Sodium cyanide (100 mg, 2.0 mmol) was added and the mixture heated to 175 °C for 1.5 h, cooled to room temperature, and poured *with care* into hydrochloric acid (20 mL, 2 N). The aqueous layer was extracted several times with ether, the combined organic phases were washed with water and brine and dried ($MgSO_4$), and the solvent was removed in vacuo. Purification by flash column chromatography (60% ethyl acetate/hexane) afforded 26 mg (64%) of phenol **40**: mp 209–210 °C; $[\alpha]^{20}_D$ +136° (c 0.089, $CHCl_3$); UV λ_{max} (EtOH) 317, 276, 229 nm (ϵ_{max} 3900, 8000, 20 700); UV λ_{max} (EtOH, OH$^-$), 372, 258, 213 nm (ϵ_{max} 6700, 17 900, 44 900); IR ($CHCl_3$) 3580 (w), 3340 (br w), 2950 (m), 1705 (vs), 1330 (m), 1275 (m), 1190 (m) cm^{-1}, ratio of absorbance at 3600 and 3350 cm^{-1} changes with concentration; NMR (250 MHz, $CDCl_3$) δ 5.88 (br s, 1 H), 3.0–2.8 (m, 4 H), 2.70–2.55 (m, 2 H), 2.22 (s, 3 H), 2.03 (m, 1 H), 1.65 (d, J = 7 Hz, 1 H), 1.50–1.00 (m, 2 H), 1.25 (s, 3 H), 0.87 (s, 3 H); electron impact mass spectrum, m/e 284.1399 (M^+, calcd for $C_{18}H_{20}O_3$, 284.1412).

Phenol 41. Using a procedure identical with that for phenol **40**, methyl ether **39** (63 mg, 0.21 mmol) afforded 35 mg (59%) of phenol **41** after flash column chromatography (20% ethyl acetate/hexane): $[\alpha]^{20}_D$ +147° (c 0.44, $CHCl_3$); UV λ_{max} (EtOH) 327, 255, 201 nm (ϵ_{max} 3400, 18 700, 11 800); UV λ_{max} (EtOH, OH$^-$) 333, 267, 206 nm (ϵ_{max} 10 000, 20 700, 46 100; IR ($CHCl_3$) 3280 (br m), 2940 (m), 1680 (vs), 1620 (m), 1590 (m), 1460 (m), 1320 (m), 1280 (s), 1190 (m) cm^{-1}, peak at 3280 cm^{-1} unaltered by changing concentration; NMR (250 MHz, $CDCl_3$) δ 9.56 (s, 1 H), 3.42 (m, 1 H), 2.95–2.60 (m, 5 H), 2.19 (s, 3 H), 2.05 (m, 1 H), 1.58 (d, J = 9 Hz, 1 H), 1.50–1.0 (m, 2 H), 1.31 (s, 3 H), 0.95 (s, 3 H); electron impact mass spectrum, m/e 284.1400 (M^+, calcd for $C_{18}H_{20}O_3$, 284.1412).

Phenol 42. To a stirred solution of the Diels–Alder adduct **18** (200 mg, 0.66 mmol) in THF (30 mL) was added 2 M HCl (7 mL). After 40 min, when no change in the TLC was apparent, the mixture was poured into water (50 mL) and extracted with ether, the combined extracts were washed with brine and dried ($MgSO_4$), and the solvent was removed in vacuo to yield a residue which upon flash column chromatography (25% ethyl acetate/hexane) afforded 134 mg (75%) of pure phenol **42**: mp 170–171 °C; $[\alpha]^{20}_D$ +65.0° (c 1.27, $CHCl_3$); UV λ_{max} (EtOH) 279, 225, 204 nm (ϵ_{max} 7000, 13 800, 20 600); UV λ_{max} (EtOH, OH$^-$) 374, 261, 215 nm (ϵ_{max} 14 200, 9500, 74 800); IR ($CHCl_3$) 3600 (m), 3380 (br m), 1670 (s), 1575 (s), 1340 (m), 1280 (m), 1225 (m), 1160 (s) cm^{-1}; NMR (250 MHz, $CDCl_3$) 5.43 (br s, 1 H), 3.15 (m, 1 H), 2.90–2.55 (m, 5 H), 2.18 (s, 3 H), 2.15–1.90 (m, 3 H), 1.62 (d, J = 9.5 Hz, 1 H), 1.40 (m, 1 H), 1.24 (s, 3 H), 1.12 (m, 1 H), 0.91 (s, 3 H); ^{13}C NMR ($CDCl_3$) 210.06 (s), 152.46 (s), 142.97 (s), 134.66 (s), 130.69 (s), 128.43 (s), 123.22 (s), 43.04 (t), 32.72 (t), 28.78 (t), 28.50 (d), 28.35 (q), 27.81 (d), 24.81 (t), 20.91 (s), 19.89 (t), 15.71 (q), 12.21 (q).

Anal. Calcd for $C_{18}H_{22}O_2$: C, 80.00; H, 8.15. Found: C, 79.82; H, 8.35.

Olefin 43. To a stirred suspension of methyltriphenylphosphonium bromide (5.00 g, 14 mmol) in dry toluene (15 mL) at room temperature under argon was added n-butyllithium (5.5 mL, 2.55 M, 14.0 mmol). After 30 min, a solution of the phenol **42** (276 mg, 1.02 mmol) in dry THF (2 mL) was added and the reaction mixture heated at reflux for 48 h. After cooling to room temperature, the orange mixture was poured into 2 N HCl (20 mL) and extracted with ether, the combined extracts were washed with brine and dried ($MgSO_4$), and the solvent was removed in vacuo to give the product. Purification by flash column chromatography (15% ethyl acetate/hexane) yielded 35 mg of recovered phenol **42** and 195 mg (81%) of olefin **43**: $[\alpha]^{20}_D$ +21.3° (c 1.48, $CHCl_3$); UV λ_{max} (EtOH) 210 nm (ϵ_{max} 22 300); UV λ_{max} (EtOH, OH$^-$) 214 nm, (ϵ 42 700); IR ($CHCl_3$) 3600 (s), 2950 (s), 1580 (m), 1455 (s), 1265 (m), 1220 (m), 1120 (s), 1090 (m), 1060 (m), 890 (s) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 5.15 (br s, 1 H), 4.76 (br s, 1 H), 4.44 (s, 1 H, OH), 3.05–2.15 (m, 4 H), 2.55 (m, 2 H), 2.18 (s, 3 H), 2.15–1.90 (m, 2 H), 1.80 (m, 1 H), 1.60 (d, J = 9 Hz, 1 H), 1.22 (s, 3 H), 0.95 (m, 1 H), 0.88 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 149.2 (s), 148.7 (s), 140.7 (s), 134.9 (s), 131.8 (s), 126.6 (s), 122.2 (s), 114.5 (t), 33.8 (t), 32.5 (t), 29.2 (t), 28.9 (d), 28.3 (q), 25.7 (d), 24.9 (t), 21.6 (t), 19.5 (s), 16.2 (q), 12.5 (q); electron impact mass spectrum, m/e 268.1824 (M^+, calcd for $C_{19}H_{24}O$, 268.1827).

Triethylsilyl Ether 47. To a stirred solution of phenol **43** (22 mg, 0.082 mmol) in dry methylene chloride (5 mL) at room temperature under argon was added dry triethylamine (0.3 mL, 2.1 mmol) followed by triethylsilyl chloride (20 μL, 0.11 mmol). After stirring at room temperature for 1 h, the mixture was poured into saturated sodium bicarbonate solution (20 mL) and methylene chloride (10 mL), the phases were separated, and the aqueous phase was extracted with methylene chloride. The solvent was removed in vacuo to give 29 mg (93%) of ether **47**: UV λ_{max} (EtOH) 211 nm (ϵ_{max} 24 000); IR ($CHCl_3$) 2950 (s), 1460 (s), 1355 (m), 1315 (m), 1290 (m), 1130 (m), 1095 (m), 1070 (m), 800 (m) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 5.14 (br s, 1 H), 4.75 (br s, 1 H), 3.05–2.80 (m, 3 H), 2.68 (m, 1 H), 2.55 (m, 2 H), 2.13 (s, 3 H), 2.10–1.85 (m, 2 H), 1.75 (m, 1 H), 1.56 (d, J = 11 Hz, 1 H), 1.21 (s, 3 H), 0.98 (t, J = 7 Hz, 9 H), 0.84 (s, 3 H), 0.9–0.8 (m, 1 H), 0.75 (q, J = 7 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 149.8 (s), 149.0 (s), 140.5 (s), 134.7 (s), 132.8 (s), 131.7 (s), 127.5 (s), 114.3 (t), 33.9 (t), 32.6 (t), 31.3 (t), 29.4 (d), 28.3 (q), 26.0 (d), 25.0 (t), 21.7 (t), 19.3 (s), 16.1 (q), 14.2 (q), 6.78 (q), 5.99 (t); electron impact mass spectrum, m/e 382.2704 (M^+, calcd for $C_{25}H_{38}OSi$, 382.2691).

Ketones 48 and 49. A stirred suspension of vacuum-dried chromium trioxide (0.52 g, 5.2 mmol) in dry CH_2Cl_2 (15 mL) was cooled to −20 °C under argon before the addition of 3,5-dimethylpyrazole (500 mg, 5.2 mmol). The reagent was allowed to form over a 15-min period at −10 °C, followed by the addition of silyl ether **47** (200 mg, 0.52 mmol) in 3 mL of dry CH_2Cl_2. The reaction mixture was stirred for 3 h and then poured into ether (40 mL) and dilute sodium hydroxide solution (30 mL). The phases were separated, and the aqueous phase was extracted with ether. The combined extracts were washed with water and brine and dried ($MgSO_4$), and the solvent was removed in vacuo to yield, after flash column chromatography (10% ethyl acetate/hexane), 70 mg (34%) of ketone **48** and 12 mg (6%) of ketone **49**.

48: $[\alpha]^{20}_D$ +59.0° (c 0.37, $CHCl_3$); UV λ_{max} (EtOH) 317, 269, 225, 200 nm (ϵ_{max} 2100, 6500, 19 400, 10 600); IR ($CHCl_3$) 1708 (s), 1570 (m), 1480 (m), 1460 (m), 1285 (s), 1120 (m) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 5.23 (br s, 1 H), 4.67 (br s, 1 H), 2.95 (m, 2 H), 2.70–2.50 (m, 4 H), 2.23 (s, 3 H), 1.80 (m, 1 H), 1.58 (d, J = 8.5 Hz, 1 H), 1.23 (s, 3 H), 1.00 (t, J = 7 Hz, 9 H), 1.00–0.80 (m, 2 H, superimposed upon t, 9 H); ^{13}C NMR ($CDCl_3$) δ 205.4 (s), 150.8 (s), 145.9 (s), 143.2 (s), 137.4 (s), 136.3 (s), 135.1 (s), 133.1 (s), 114.8 (t), 37.0 (t), 33.6 (t), 28.7 (d), 28.2 (q), 26.2 (d), 22.7 (t), 21.5 (t), 19.3 (s), 16.0 (q), 14.8 (q), 6.68 (q), 5.99 (t); electron impact mass spectrum, m/e 396.2456 (M^+, calcd for $C_{25}H_{36}O_2Si$, 396.2485.

49: $[\alpha]^{20}_D$ +58.0° (c 0.38, $CHCl_3$); UV λ_{max} (EtOH) 321, 272, 228, 206 nm (ϵ_{max} 2700, 10 900, 20 500, 17 900); IR ($CHCl_3$ solution) 1700 (s), 1580 (m), 1455 (m), 1445 (m), 1310 (m), 1285 (m), 1110 (s) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 5.26 (br s, 1 H), 4.82 (br s, 1 H), 3.08 (m, 1 H), 2.75 (m, 1 H), 2.70–2.50 (m, 4 H), 2.18 (s, 3 H), 1.82 (m, 1 H), 1.64 (d, J = 8.5 Hz, 1 H), 1.24 (s, 3 H), 1.00 (t, J = 7 Hz, 9 H), 1.0–0.8 (m, 2 H), 0.85 (s superpimposed upon dq, 9 H); chemical ionization mass spectrum, m/e 397.2574 (MH^+, calcd for $C_{25}H_{37}O_2Si$, 397.2563).

Triethylsilyl Jatropholones A and B (50 and 51). To a stirred solution of diisopropylamine (0.73 mL, 5 mmol) in dry THF (5 mL) at −20 °C under argon was added n-butyllithium (1.96 mL, 5 mmol). In a separate flask, a solution of ketone **48** (37 mg, 0.097 mmol) in 4 mL of THF was cooled to −78 °C under argon before the addition of the solution of LDA (150 μL, 0.098 mmol). The enolate was allowed to form over 30 min at

-78 °C, followed by the addition of methyl iodide (20 μL), and then the mixture was allowed to warm slowly to room temperature. The colorless solution was poured into water/ether, and the phases were separated. The aqueous phase was extracted with ether, and the combined extracts were washed with brine and dried ($MgSO_4$), and the solvent was removed in vacuo. Flash column chromatography (10% ethyl acetate/hexane) afforded a mixture of the α- and β-epimers (30 mg, 78%). The epimers were separated by HPLC (4% ethyl acetate/hexane) to afford the individual isomers in a 74:26 (α:β) ratio.

50: $[\alpha]^{20}_D$ +51° (*c* 0.036, $CHCl_3$); UV λ_{max} (EtOH) 316, 269, 225 nm (ϵ_{max} 2500, 8000, 23 200); IR ($CHCl_3$) 2950 (s), 1710 (s), 1580 (w), 1565 (w), 1460 (s), 1350 (m), 1335 (m), 1285 (s), 1235 (m), 1125 (s), 1000 (m), 910 (s) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 5.20 (br s, 1 H), 4.68 (t, *J* = 2 Hz, 1 H), 3.29 (dd, *J* = 15, 7 Hz, 1 H), 2.8-2.6 (m, 3 H), 2.48 (dd, *J* = 15, 4 Hz, 1 H), 2.23 (s, 3 H), 1.82 (m, 1 H), 1.58 (d, *J* = 9 Hz, 1 H), 1.27 (d, *J* = 7 Hz, 3 H), 1.23 (s, 3 H), 1.1-0.8 (m, 2 H), 1.0 (t, *J* = 7 Hz, 9 H), 0.85 (s superimposed upon 2d, 9 H); electron impact mass spectrum, *m/e* 410.2604 (M^+, calcd for $C_{26}H_{38}O_2Si$, 410.2641).

51: $[\alpha]^{20}_D$ +67.1° (*c* 0.098, $CHCl_3$); UV λ_{max} (EtOH) 318, 270, 225 nm (ϵ_{max} 2050, 6300, 18 000); IR ($CHCl_3$) 2960 (s), 1710 (s), 1570 (m), 1450 (m), 1290 (s), 1030 (m) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 5.24 (br s, 1 H), 4.68 (br s, 1 H), 3.19 (dd, *J* = 15, 7 Hz, 1 H), 2.70-2.48 (m, 4 H), 2.24 (s, 3 H), 1.83 (m, 1 H), 1.59 (d, *J* = 9 Hz, 1 H), 1.28 (d, *J* = 7 Hz, 3 H), 1.23 (s, 3 H), 1.0 (m, 9 H), 1.0-0.8 (m, 2 H), 0.85 (s superimposed upon dq, 9 H); electron impact mass spectrum, *m/e* 410.2626 (M^+, calcd for $C_{26}H_{38}O_2Si$, 410.2641).

Jatropholone B (2). To a stirred solution of silyl ether **51** (6 mg, 0.015 mmol) in dry THF (3 mL) at room temperature under argon was added tetra-*n*-butylammonium fluoride (10 μL, 1 M in THF). After 1 min, the reaction mixture was poured into water and extracted with ether, the combined extracts were washed with brine and dried ($MgSO_4$), and the solvent was removed in vacuo to afford, after flash column chromatography (33% ethyl acetate/hexane), 3.9 mg (88%) of jatropholone B: mp 226-228 °C [lit.[3] mp 228-230 °C]; $[\alpha]^{20}_D$ +77.0° (*c* 0.141, $CHCl_3$) [authentic sample[41] +80.3° (*c* 0.128, $CHCl_3$)].

Jatropholone A (1). Using a procedure identical with that for jatropholone B (**2**), 7 mg of silyl ether **50** afforded 4.5 mg of jatropholone A: mp 215-218 °C [lit.[3] mp 218-220 °C]; $[\alpha]^{20}_D$ +102° (*c* 0.095) [authentic sample[41] +107.2° (*c* 0.070, $CHCl_3$)].

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Conformations of the 8-Methylated and Unmethylated Ribohexamer r(CGCGCG)$_2$

Shashidhar N. Rao and Peter A. Kollman*

Contribution from the Department of Pharmaceutical Chemistry, University of California, San Francisco, California 94143. *Received February 4, 1985*

Abstract: Molecular mechanical calculations have been carried out on r(CGCGCG)$_2$, r(C-M^{8}G-C-m^{8}G-C-m^{8}G)$_2$, d(CGCGCG)$_2$, and d(C-m^{8}G-C-m^{8}G-C-m^{8}G)$_2$ in A, B, and Z_I forms of polynucleotides. To our knowledge, this is the first atomic level molecular mechanical study of double-stranded RNA in the three polymorphic forms, and detailed structures are presented for the energy-refined models. The calculated energies when corrected for artifacts inherent in a model for RNA and DNA without inclusion of specific hydration are in general agreement with experimental results. Specifically, the B form is more stable than the A form in DNA, the reverse being true in RNA, and the counterion condensation promotes the B to Z transition in DNA and (with more difficulty) an A to Z transition in RNA. Further, 8-methylation of guanine bases potentiates an A to Z transition in RNA and, to a smaller extent, a B to Z transition in DNA. The effect of 8-methylation on promoting the A to Z transition in RNA can be attributed to an unfavorable steric interaction of the 8-methyl group with the backbone in the A structure, reducing favorable base-stacking interactions in this structure.

Oligoribonucleotides have been the targets of several recent studies by CD-ORD and NMR methods. Following the discovery of a novel left-handed Z structure for d(CGCGCG)$_2$ in the solid state,[1] and experimental data that suggested such a conformation in solution studies,[2-5] its ribo counterpart, r(CGCGCG)$_2$, has been analyzed spectroscopically to explore the possibilities of such unusual conformations in RNA structures. Two-dimensional NOE, CD, and ORD studies on this hexaribonucleotide reveal an A form, while it was concluded that the earlier predicted Z form was unlikely even at high salt concentrations.[6-8] No B to Z or A to Z transitions were observed. However, recent investigations of poly(G-C)·poly-(G-C) by NMR, CD, and absorbance techniques[9,10] have found a transition from the A form to the Z form at high salt (6 M $NaClO_4$) for this polyribonucleotide, CD-ORD and NMR studies on modified (8-substituted) oligoribonucleotides r(C-br^{8}G-C-br^{8}G) and r(C-m^{8}G-C-m^{8}G) have also found Z-like forms at both low and high salt concentrations.[11] These studies stimulated us to carry out molecular mechanics calculations on double-stranded RNA with both the normal and substituted guanines. To our knowledge, this is the first application of molecular mechanical methods to double-stranded RNAs in

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